REMARKS

Reconsideration and withdrawal of the rejections set forth in the Final Office Action dated November 27, 2006 are respectfully requested. A separate petition for a three-month extension of time accompanies this amendment, to extend the period for reply from July 29, 2007 (two months from the May 29, 2007 filing of a Notice of Appeal) to October 29, 2007

I. Amendments

Claims 1-4, 12, 13, 17 and 22 have been amended solely for clarification, and not for purposes of overcoming any art. Basis for certain clarifications is set forth below.

Claims 1 and 17: basis for clarifying that the methods relate to "extended" release dosage forms is on, for example, paragraph [0011]. Basis for the clarification that a disintegration test is used to obtain a drug release profile is found, for example, in paragraph [0008]. In claim 17, basis for reference to "stomach" is found, for example, in paragraph [0039], and basis for the clarification that the polymer swells "upon absorption" is found, for example, in paragraph [0061].

Claims 12 and 13: basis for the clarification that the active agent is "water" insoluble, sparing soluble, or soluble is found, for example, in the abstract, and in paragraph [0099].

Claims 27-35 have been added and find basis as follows. Claims 27, 29, 30, 31, 32, and 33 find basis in paragraph [0124]; claim 28 finds basis in paragraph [0121]; and claims 34 and 35 find basis in paragraph [0121].

Accordingly, claims 1-35 are pending in this application. No new matter has been added by these amendments.

II. Rejections Under 35 U.S.C. § 112, first paragraph

Claims 1-26 were rejected under 35 U.S.C. §112, first paragraph as allegedly containing subject matter not sufficiently described in the specification to convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. In particular, the Examiner asserts that the invention is directed to a method for formulating tablet or capsule dosage forms, and that the deletion of

"wherein the dosage form is a tablet" from claim 1 broadens the claim to include other dosage forms that were not contemplated at the time of filing.

This rejection is respectfully traversed in view of the following.

Applicants direct the Examiner to the claims as originally filed, where the phrase "wherein the dosage form is a tablet" was not recited in original independent claim 1 or claim 17. Because the claims as originally filed did not recite the noted phrase, clear basis and support for pending claims 1 and 17 are present in the application as filed.

Accordingly, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §112, first paragraph.

III. Rejections Under 35 U.S.C. § 103

Claims 1-11 were rejected under 35 U.S.C. §103 as allegedly obvious over Mehra *et al.*, U.S. Patent No. 5,830,576 ("Mehra") in view of Wagner, chapters 11-21, Biopharmaceutics and Relevant Pharmacokinetics (Drug Intelligence Publications, Hamilton, Il 1971; "Wagner").

Claims 1-26 were rejected under 35 U.S.C. §103 as allegedly obvious over Franz *et al.*, U.S. Patent No. 5,232,704 ("Franz"), in view of O'Neill *et al.*, U.S. Patent No. 4,704,405 ("O'Neill"), and in further view of Wagner.

These rejections are respectfully traversed for the following reasons.

A. The Present Claims

The present claims, as embodied in pending independent claim 1, are directed to a method for selecting an extended release dosage form. The method includes a) preparing a plurality of different candidate dosage forms each comprising at least one biocompatible, hydrophilic polymer and a pharmacologically active agent incorporated therein; b) obtaining an *in vitro* drug release profile for each candidate dosage form in an aqueous medium using a disintegration test; c) comparing the *in vitro* drug release profiles obtained in step (b), and determining which of the *in vitro* drug release profiles correlates most closely with a desired *in vivo* drug release profile; and d) selecting the dosage form of (c) to develop for administration to a patient.

The present claims, as embodied in pending independent claim 17, are directed to a method for delivering a pharmacologically active agent to a patient over an extended period of time. The method includes administering to a patient, in whom the fed mode has been induced, an extended release oral dosage form. Similar to the features of claim 1, the dosage form is selected by subjecting the dosage form to a disintegration test and determining that the dosage form has an *in vitro* active agent release profile that correlates most closely with a desired *in vivo* active agent release profile.

B. The Applied Art

MEHRA describes particulate blends compressed in dosage forms, such as tablets, for delivery of pesticides and other agricultural chemicals for home, garden and other applicable venues requiring use of biocides (col. 4, lines 59-67). Mehra discloses that a desirable hardness level (tensile strength) for the solid dosage forms is about 3-15 kg/cm^2 so that the tablets are "hard enough to resist chalking and breaking during normal handling but readily disintegrate in an aqueous medium" (col. 2, lines 30-32). Mehra discloses that rapid disintegration provides the biocide tablets with a "surprisingly improved propert[y]" (col. 5, lines 6-14). In testing their examples, Mehra used a disintegration test to measure the time from when the tablet began to disintegrate to the time point of full disintegration (e.g., col. 5, lines 33-38).

WAGNER describes established teachings on methods of determining *in vivo* and *in vitro* disintegration and dissolution testing of a variety of dosage forms and methods for interpretation and correlation of the resulting data. In one example with reference to Chapman *et al.*[1], Wagner discusses obtaining a drug release profile in a disintegration tester to determine the predictive potential of disintegration testing for evaluating a tablet's drug release properties (Chapter 13, page 82, col. 1, lines 14-36).

FRANZ describes a sustained release capsule including an uncompressed bi-layer formulation that includes a drug release layer and a buoyancy layer. The drug release layer and the buoyancy layer are formulated to ensure cohesion of the two layers for an extended

[1] Chapman *et al.*, 1956. The Relationship between *in vitro* Disintegration Time of Sugar Coated Tablets and Physiological Availability of Sodium p-Aminosalicylate. *J. Am. Pharm. Assoc. Sci. Ed.* **45**: 374-378.

period of time such that the drug is released in the stomach by a combination of diffusion and erosion of the drug release layer (col. 3, lines 14-22; col. 4, lines 55-59). Bi-layer cohesion and erosion of the drug layer was tested using disintegration testing (col. 7, lines 4-12). *In vitro* release profiles from the capsule were determined using the paddle dissolution test (col. 19, lines 12-14; col. 20, lines 22-26) and, in some embodiments, subsequently compared to the erosion profiles from the disintegration tests to confirm consistency between drug release and erosion of the drug release layer (col. 9, lines 47-56; col. 19, lines 12-14).

O'NEILL describes a combination of the non-steroidal anti-inflammatory drug sulindac and a base. The combination is formulated into a tablet that delivers the drug into the duodenum (col. 1, line 65 – col. 2, line 4).

C1(i). Analysis: The Legal Standard

According to the M.P.E.P. § 2143, "to establish a prima facie case of obviousness, three basic criteria must be met." The third criterion is that "the prior art references (or references when combined) must teach or suggest all the claim limitations."

C1(ii). Addressing the Examiner's Position on Mehra and Wagner

The Examiner concedes that "Mehra does not specifically disclose correlation between release profile and disintegration and relating disintegration with selecting an optimized controlled release dosage form (November 27, 2006 Office action, page 4, lines 2-4)," yet asserts that "it would have been obvious to one of ordinary skill in the art at the time of the invention was made to prepare the tablet dosage form of Mehra by determining and obtaining disintegration and/or dissolution data in the decision to formulate the desired dosage form....that would further lead to the type of release profile desired", (November 27, 2006 Office Action, page 4). The Applicants respectfully disagree.

The pending claims recite that drug release profiles for candidate dosage forms are obtained using a disintegration test, the profiles are compared, and a determination is made as to which profile corresponds most closely with a desired *in vivo* drug release profile. The features of using drug release profiles, obtained using a disintegration test, being compared to a desired *in vivo* release profile followed by a determination as to which profile correlates

most closely with a desired *in vivo* release profile are not shown or suggested by either of Mehra or Wagner, alone or in combination.

Mehra teaches using a disintegration tester to measure disintegration time of dosage forms (e.g., col. 5, lines 33-38), rather than drug release profiles of dosage forms. Wagner teaches using a disintegration tester to measure a dosage form's disintegration time (chapter 11, pages 69-71) and using a dissolution method for obtaining drug release profiles (see Chapter 17 for a variety of methods). Wagner cites to Chapman *et al.* as disclosing measuring the amount of drug in solution as a function of time for quick release tablets subjected to a standard disintegration test (chapter 13, page 82, col. 1, lines 14-18). The kinetic profiles obtained in the disintegration test were then plotted against the disintegration time to determine the predictive potential of disintegration testing for determining a tablet's drug release properties (chapter 13, page 82, col.1, lines 18-26).

In direct contrast to the claimed features, Wagner does not teach or suggest comparing drug release profiles obtained from a disintegration test to determine which profile correlates most closely with a desired *in vivo* drug release profile. The *in vitro – in vivo* correlations discussed in Wagner are limited. For example, Wagner discloses correlating *in vitro* disintegration time, obtained in a disintegration test, to *in vivo* disintegration time (Chapter 13, page 79, col. 1, ¶ 2 – page 81, col. 1, ¶ 2). Wagner also discloses correlating *in vitro* dissimilation release profiles, obtained from dissimilation testing, to *in vivo* release profile data (Chapter 19, page 121, col. 1, ¶ 2 - page 124, col. 2, ¶ 3). In one example and with reference to Chapman *et al.*, Wagner discloses correlating *in vitro* release profiles, obtained during a disintegration test, with *in vitro* disintegration time obtained during the same disintegration test (Chapter 13, page 82, col. 1, lines 14-18). There is a clear absence in the teachings of Wagner of examples and/or methods for correlating *in vitro* disintegration release profiles, obtained using a disintegration test, to *in vivo* drug release profiles.

In the claimed methods, *in vitro* drug release profiles for candidate dosage forms are obtained using a disintegration test, compared, and a determination made as to which profile corresponds with a desired *in vivo* drug release profile.

The combined teachings of Mehra and Wagner fail to show or suggest such a method. The teaching in Mehra with respect to use of a disintegration test is limited to measuring the disintegration time of the tablets (e.g., col. 5, lines 33-38), not a drug release

profile. As described above, Wagner discloses three distinct methods of correlation of data sets: *in vitro* disintegration time with *in vivo* disintegration time; *in vitro* dissimilation release profiles with *in vivo* release profiles; and *in vitro* release profiles with *in vitro* disintegration time (Chapters 13 and 19). None of this disclosure in Wagner shows or suggests obtaining a drug release profile using a disintegration test, comparing the profiles, and determining which profile correlates most closely with a desired *in vivo* drug release profile.

Considering the teaching of Mehra and Wagner in combination, drug release profiles, of drug forms subjected to disintegration, have not been correlated with desired *in vivo* release profiles. Furthermore, because these cited references lack any such analysis or methods of correlation, the cited references are also clearly absent disclosure for the determination of which of the *in vitro* release profiles correlates most closely with a desired *in vivo* drug release profile.

Accordingly, the combined teachings of Mehra and Wagner fail to establish a *prima facie* case of obviousness. Withdrawal of the rejection is respectfully requested.

C2. Analysis: Rejection Based on Franz, O'Neill and Wagner

According to the M.P.E.P. § 2143, "to establish a prima facie case of obviousness, three basic criteria must be met." The third criterion is that "the prior art references (or references when combined) must teach or suggest all the claim limitations."

As noted above, the claimed methods involve selecting an extended release dosage form from steps that include obtaining an *in vitro* drug release profile for each candidate dosage form in an aqueous medium using a disintegration test, comparing the *in vitro* drug release profiles obtained and determining which of the *in vitro* drug release profiles correlates most closely with a desired *in vivo* drug release profile.

Franz discloses a sustained release capsule including an uncompressed bi-layer formulation that includes a drug release layer and a buoyancy layer (col. 3, lines 14-22). O'Neill discloses sulindac formulated in combination with a base into a tablet (col. 1, line 65 – col. 2, line 4). Wagner discloses disintegration tests to measure the disintegration of dosage forms and dissolution tests to measure drug release profiles of dosage forms (see Chapters 11 and 17). Wagner also discloses methods for interpretation and correlation of *in vitro* and *in vivo* data (see Chapters 13 and 19-20).

Absent from the combined teachings of Franz, O'Neill and Wagner is the claimed feature of comparing drug release profiles obtained using a disintegration test and determining which profile most closely correlates with a desired *in vivo* drug release profile. Neither Franz nor O'Neill disclose obtaining a drug release profile using a disintegration test or determining which profile most closely correlates with a desired *in vivo* drug release profile. As described above, Wagner discloses three distinct methods of correlation of data sets: *in vitro* disintegration time with *in vivo* disintegration time; *in vitro* dissimilation release profiles with *in vivo* release profiles; and *in vitro* release profiles with *in vitro* disintegration time (Chapters 13 and 19). Wagner, with reference to Chapman *et al.* (Chapter, page 82, col. 1, lines 14-18), discloses obtaining a drug release profile in a disintegration tester, yet fails to describe comparing these profiles to determine which profile most closely correlates with a desired *in vivo* drug release profile. Accordingly, the combination of the cited documents fails to show or suggest each and every claim element, and a *prima facie* case of obviousness has not been established.

For clarity of the record, Applicants note an erroneous statement in the Final Office Action, where the Examiner asserts that Franz discloses release profiles of capsules of active agents determined by disintegration (November 27, 2006 Office action, page 8). The Examiner is directed to Col. 7, lines 4-12 in Franz, where bi-layer cohesion and erosion of the drug layer is tested using disintegration testing. It is clear from this disclosure that Franz used a disintegration test to measure disintegration of the capsules, not to obtain an active agent release profile. In fact, Franz discloses obtaining *in vitro* measured activity release profiles from the capsules using the paddle dissolution test (col. 9, lines 47-56; col. 19, lines 12-14).

Accordingly, since the combined teachings of the cited documents fail to show or suggest all of the claim elements, the Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §103.

IV. Additional Matters

On page 9 of the Final Office Action, the Examiner notes that the Applicants' representative presented arguments against a rejection under 35 U.S.C. § 102 when no § 102 rejection was presented in the Office Action dated February 28, 2006. The Applicants direct the Examiner to page 6, lines 1-5 of the Amendment dated August 18, 2006 where

Applicants noted that due to the removal of the claim limitation that the dosage form is a table, "Applicants are readdressing the Franz et al. anticipation rejection from the Office Action of August 30, 2005...".

In the event any question remains as to whether the pending claims are novel over Franz, the following remarks are provided.

As described above, Franz discloses a disintegration test for measuring disintegration of the capsules (col. 7, lines 4-12), not to obtain an active agent release profile as presently claimed. Moreover, Franz does not teach comparing the *in vitro* release profiles to determine which profile correlates with a desired *in vivo* release profile. Accordingly, Franz fails to meet the requirement for anticipation for at least these reasons, and the § 102 rejection should not be re-presented.

V. Conclusion

In view of the foregoing, the claims pending in the application comply with the requirements of 35 U.S.C. § 112 and patentably define over the applied art. A Notice of Allowance is, therefore, respectfully requested. If the Examiner has any questions or believes a telephone conference would expedite prosecution of this application, the Examiner is encouraged to call the undersigned at (650) 838-4402.

Respectfully submitted,
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Date: 10/29/07

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